JACC: CARDIOVASCULAR INTERVENTIONS VOL. 13, NO. 13, 2020

PUBLISHED BY ELSEVIER

CORONARY

Long-Term Outcomes of Complete Revascularization With Percutaneous Coronary Intervention in Acute Coronary Syndromes

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the long-term outcomes of patients with acute coronary syndromes (ACS) with multivessel disease undergoing percutaneous coronary intervention (PCI).

BACKGROUND Controversy exists regarding the benefit of multivessel PCI across the spectrum of ACS.

METHODS A total of 9,094 patients with ACS and multivessel disease (≥70% stenosis in 2 or more major epicardial vessels) undergoing PCI from the Alberta COAPT (Contemporary Acute Coronary Syndrome Patients Invasive Treatment Strategies) registry (April 1, 2007, to March 31, 2013) were reviewed. Comparisons were made between patients who underwent complete revascularization and those with incomplete revascularization. Complete revascularization was defined as multivessel PCI with a residual angiographic jeopardy score ≤10%. Associations between revascularization status and all-cause death or new myocardial infarction (primary composite endpoint) and all-cause death, new myocardial infarction, or repeat revascularization (secondary composite endpoint) were evaluated.

RESULTS Of the study cohort, 66.0% underwent complete revascularization. Compared with incomplete revascularization, the primary composite endpoint occurred less frequently with complete revascularization (event rate within 5 years 15.4% vs. 22.2%; inverse probability-weighted hazard ratio [IPW-HR]: 0.78; 95% confidence interval [CI]: 0.73 to 0.84; $p < 0.0001$). The secondary composite endpoint was less likely to occur with complete revascularization (event rate within 5 years 23.3% vs. 37.5%; IPW-HR: 0.61; 95% CI: 0.58 to 0.65; $p < 0.0001$). Complete revascularization was associated with a reduction in all-cause death (IPW-HR: 0.79; 95% CI: 0.73 to 0.86; $p = 0.0004$), new myocardial infarction (IPW-HR: 0.76; 95% CI: 0.69 to 0.84; $p < 0.0001$), and repeat revascularization (IPW-HR: 0.53; 95% CI: 0.49 to 0.57; $p < 0.0001$).

CONCLUSIONS Results from this large contemporary registry of patients with ACS and PCI for multivessel disease suggest that complete revascularization occurs commonly and is associated with improved clinical outcomes (including survival) within 5 years. (J Am Coll Cardiol Intv 2020;13:1557–67) © 2020 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

Manuscript received December 6, 2019; revised manuscript received February 25, 2020, accepted April 14, 2020.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2020.04.034

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

aOR = adjusted odds ratio

CI = confidence interval

CV = cardiovascular

HR = hazard ratio

ICD-10 = International Classification of Diseases-10th Revision

IPW-HR = inverse probability-weighted hazard ratio

IQR = interquartile range

K-M = Kaplan-Meier

MI = myocardial infarction

NSTEACS = non-ST-segment elevation acute coronary syndrome(s)

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Approximately one-half of patients with ST-segment elevation myocardial infarction (STEMI) and two-thirds of those with non-ST-segment elevation acute coronary syndromes (NSTEACS) present with additional stenosis remote to the culprit infarct-related artery. In patients with acute coronary syndromes (ACS) with multivessel disease, an opportunity for additional nonculprit revascularization exists (1–4). However, the merits of complete revascularization, of both culprit and nonculprit vessels, compared with culprit-only or incomplete revascularization continue to be debated with percutaneous coronary intervention (PCI) across the spectrum of ACS. One apparent advantage of incomplete revascularization is that it addresses the ruptured or eroded plaque and avoids periprocedural complications associated with nonculprit intervention. In contrast, complete revascularization may alter future cardiac events, as has been recently demonstrated in STEMI (5).

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Accordingly, using a large population-based cohort of patients with ACS with multivessel disease undergoing PCI, we compared demographics, comorbidities, evidence-based medication use, and long-term clinical outcomes in patients with complete revascularization and incomplete revascularization. We identified patient factors associated with complete revascularization and examined the relationship between the extent of incomplete revascularization and long-term outcomes.

METHODS

PATIENT POPULATION. Patients enrolled in the Alberta COAPT (Contemporary Acute Coronary Syndrome Patients Invasive Treatment Strategies) registry have been previously described (6). In brief, our study cohort consisted of all patients hospitalized with ACS between April 1, 2007, and March 31, 2013, in Alberta, Canada. International Classification of Diseases-10th Revision (ICD-10) codes were used to identify hospitalizations with primary diagnoses of non-ST-segment elevation myocardial infarction [NSTEMI] (I21.4), unstable angina (I20.0), or STEMI (I21.0, I21.1, I21.2, and I21.3) in the Discharge Abstract Database. Concurrent hospitalizations occurring within 24 h of each other were considered to be part of the same episode. The first ACS episode during our study time period was considered to be the index episode. The Discharge Abstract Database was linked, using a unique patient identifier, to the APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease) registry, which includes detailed demographic, clinical, and anatomic data for all patients who undergo cardiac catheterization in Alberta (7). This is a prospective dataset in which coronary anatomy and severity of disease are captured at the time of coronary angiography (diagnostic) and following PCI by the interventional cardiologist. Embedded within APPROACH is the Coronary Artery Reporting and Archiving Tool, which automatically produces an angiographic jeopardy score on the basis of position and degree of coronary stenoses. Quality audits are performed to ensure the accuracy, completeness, and integrity of the data. Patients undergoing PCI for multivessel disease were retained for the analysis. Multivessel disease was defined on the basis of the Duke Coronary Artery Disease Index as involving 2 or more major epicardial vessels with a diameter stenosis ≥70% or left main vessel ≥50%. Patients with prior coronary artery bypass grafting or who underwent coronary artery bypass grafting within 1 month were excluded.

DEFINITIONS OF COMPLETE REVASCULARIZATION AND INCOMPLETE REVASCULARIZATION. Consistent with previous studies and expert clinical opinion, complete revascularization was defined as <10% of myocardium at risk calculated using the post-PCI angiographic jeopardy score (8,9). The angiographic jeopardy score used in the present study is based on a scoring system (10), with modifications from pathological data (11,12). In brief, jeopardized territories are those supplied by vessels with ≥70% stenoses (>50% stenosis of the left main coronary artery). All jeopardized territories are summed, for a maximum score of 100. This angiographic jeopardy score has been well validated and was chosen for residual myocardial jeopardy as it has been shown previously to provide additional independent prognostic information compared with the Jeopardy Score from Duke University and the Myocardial Jeopardy Index from BARI (Bypass Angioplasty Revascularization Investigation) in a comparative study (13). A detailed description of the score is provided in the Supplemental Appendix.

The assessment of complete revascularization incorporated all PCI procedures that occurred within the month after the ACS event, in order to account for staged PCI procedures. To account for survivor bias, patients who died within this time period (i.e., in the

first month after the index ACS event) were excluded from the analysis, as they did not have an opportunity to undergo complete revascularization. Among survivors, the PCI procedure that was associated with the lowest angiographic jeopardy score was used to identify patients with complete revascularization. Depending on the timing of when complete revascularization was achieved during the 1-month window, patients were further classified as "no staging" when achieved on the same index PCI date, "staged in hospital" if performed on a later day but before discharge from index hospitalization, and "staged outpatient" when performed after discharge from index hospitalization.

Patients who did not achieve <10% of myocardium at risk after any PCI procedure within 1 month following the index ACS event were considered as having undergone incomplete revascularization. In addition to this dichotomized definition, we examined the extent of incomplete revascularization as a continuous variable on the basis of the angiographic jeopardy score.

DEFINITIONS OF COMORBIDITIES. Previously established ICD-10 codes were used to identify comorbidities, including chronic heart failure, prior myocardial infarction (MI), dementia, diabetes, cerebrovascular disease, cancer, renal disease, peripheral vascular disease, chronic obstructive pulmonary disease, and atrial fibrillation (14). Comorbidities were considered to be present at baseline if they were coded in any of the hospitalizations during the index episode. Furthermore, the Charlson comorbidity score (15) was applied to summarize the patient's comorbidity burden.

EVIDENCE-BASED MEDICATION USE. The Pharmaceutical Information Network database of pharmaceutical claims was available as of April 1, 2008. In patients who were discharged from index ACS hospitalization after this date, we examined their pharmaceutical claims in the 6-month post-discharge period to identify prescription of the following cardiovascular (CV)-specific drugs: angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers, calcium-channel blockers, lipid-modifying agents, spironolactone, and $P2Y_{12}$ receptor antagonists, acknowledging that acetylsalicylic acid use cannot be quantified because of its nonprescription use.

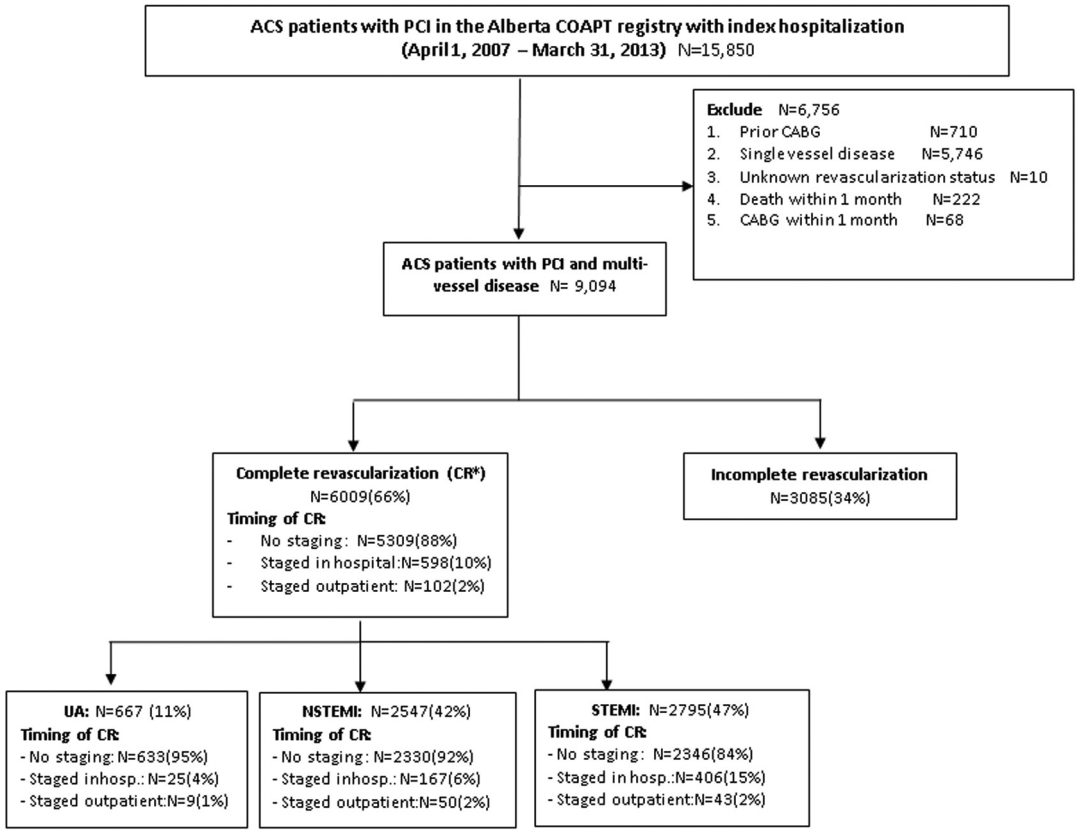
CLINICAL OUTCOMES. The primary clinical outcome of interest was a composite of all-cause mortality or new MI. Time to event was calculated from the PCI in which complete revascularization was achieved or the last PCI occurring within 1 month after the index ACS event, whichever came first. The secondary outcome of interest was time to composite of all-cause mortality, new MI, or repeat revascularization. Other outcomes included: 1) time to individual secondary outcome components; 2) time to a composite of CV-specific mortality or new MI; and 3) time to CV mortality. CV mortality was identified on the basis of ICD-10 codes for the circulatory system (ICD-10 codes I00 to I99) on the death certificate.

STATISTICAL ANALYSIS. Data on baseline characteristics of patients, including demographics, comorbidities, type of ACS at presentation, and evidence-based medication use, were compared between the complete revascularization and incomplete revascularization groups. Continuous variables are summarized as mean ± SD or median (interquartile range [IQR]) and compared between the groups using Student's *t*-test and the Mann-Whitney *U* test, respectively. Categorical variables are summarized as counts and percentages and were compared by applying the Pearson chi-square test.

A multivariable logistic regression model with stepwise selection (with a significance level of 0.3 for entry and 0.1 for staying in the model) was used to evaluate the independent associations between baseline characteristics, including sex, age (per 10 years), type of ACS at presentation, and comorbidities (MI within the past year, heart failure, hypertension, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, diabetes, peripheral vascular disease, renal disease, cancer, and atrial fibrillation) and the odds of complete revascularization. Odds ratios and 95% confidence intervals (CIs) were estimated as measures of the association.

The Kaplan-Meier (K-M) method was used to estimate the clinical event rates, and K-M curves were used to graphically depict event-free survival over long-term follow-up. Cox proportional hazard models were used to examine whether the complete revascularization and incomplete revascularization patient groups differed with regard to the primary and secondary clinical outcomes. Validity of the proportionality assumption was checked through time-dependent covariates in the model and its significance tested. Both unadjusted and adjusted analyses were performed to estimate the hazard ratios (HRs) and 95% CIs. The adjusted analysis was based on the inverse probability weighting approach, in which the propensity for each patient to have undergone complete revascularization was first estimated using a multivariable logistic regression and later used as a weight function in the Cox regression models. The same set of clinically relevant baseline

FIGURE 1 Study Cohort



*Based on the minimum JEOPARDY score within a period of 1 month from the index hospitalization. Therefore, the follow up of a patient starts from the last PCI date within the 1 months period. ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; COAPT = Contemporary Acute Coronary Syndrome Patients Invasive Treatment Strategies; CR = complete revascularization; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

variables described earlier was included in the multivariable logistic regression model to estimate the propensity score. Modeling assumptions of linearity of continuous risk factors were assessed. Flexible modeling that relaxed the linearity was applied when the assumption failed.

In addition to examining the relationship between myocardium at risk as a dichotomous variable (≤10%, complete revascularization; >10%, incomplete revascularization), we examined the association between the angiographic jeopardy score following PCI (i.e., extent of incomplete revascularization) as a continuous variable and the primary outcome of all-cause death or recurrent MI using cubic splines with 95% CIs. For this analysis, a jeopardy score of 10% was taken as the reference (HR: 1).

To evaluate whether the effect of complete revascularization varied according to specific patient groups, a series of planned subgroup analyses were performed after formal tests of interactions (a priori). The patient subgroups were divided according to patient sex (female or male), age (≥75 or <75 years), coronary anatomy (2-vessel disease, 3-vessel disease, or left main with or without 3-vessel disease), ACS type (unstable angina, NSTEMI, or STEMI), diabetes (yes or no), and renal disease (yes or no). Each subgroup analysis was adjusted for age, sex, ACS type, and comorbidity burden as summarized by Charlson comorbidity score, except where one of these was the subgroup variable of interest. In addition, among complete revascularization patients, we examined the association between the timing of complete

revascularization (index or subsequent staged procedure), overall and among ACS subtypes, and the primary outcome.

A 2-sided p value <0.05 was regarded as indicating statistical significance. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina). The health ethics board of the University of Alberta approved this study.

RESULTS

As seen in Figure 1, 15,850 patients who presented with ACS and underwent cardiac catheterization during the hospitalization were selected between April 1, 2007, and March 31, 2013. Of these, 6,756 were excluded because of prior coronary artery bypass grafting, single-vessel disease, unknown revascularization status, or death before the 1-month staging window period had ended. Additionally, patients who underwent coronary artery bypass grafting within 1 month of ACS were excluded, as jeopardy scores following revascularization for these patients were not available. The final cohort consisted of 9,094 patients with ACS with PCI and multivessel disease, of whom 6,009 (66.0%) underwent complete revascularization. Over a median follow-up period of 64 months (IQR: 48 to 82 months; maximum 105 months), 16.1% complete revascularization patients (n = 967) underwent repeat revascularization (PCI, 86% [n = 835]; coronary artery bypass grafting, 16.6% [n = 161]). In contrast, 25.0% incomplete revascularization patients (n = 772) underwent repeat revascularization, with a slightly higher proportion undergoing coronary artery bypass grafting (PCI, 79% [n = 611]; coronary artery bypass grafting, 24.6% [n = 190]). Median time to subsequent revascularization in complete revascularization patients was 23.0 months (IQR: 7.2 to 49.1 months) compared with 10.2 months (IQR: 2.8 to 29.7 months) in incomplete revascularization patients.

Of the 222 excluded patients who did not survive the 1-month staging window period (regardless of revascularization status), comparisons were made with those included in the present study. These patients were older, were more likely to be female and to present with STEMI, and had significantly higher rates of heart failure, cerebrovascular disease, renal disease, and cancer (Supplemental Table S1). Median time to death was 4 days (IQR: 1 to 11 days).

BASELINE CHARACTERISTICS. Baseline characteristics in the complete revascularization and incomplete revascularization groups are outlined in Table 1.

TABLE 1 Patient Characteristics With Complete Revascularization or Incomplete Revascularization

	Complete Revascularization (n = 6,009)	Incomplete Revascularization (n = 3,085)	p Value
Type of ACS			
UA	11.1	10.0	0.1253
NSTEMI	42.4	41.0	0.1957
STEMI	46.5	49.0	0.0258
Demographics			
Age, yrs	62.7 ± 11.7	64.7 ± 12.4	<0.0001
Female	23.2	23.4	0.8397
Comorbidities			
Prior MI	8.2	13.3	<0.0001
Heart failure	5.8	9.6	<0.0001
Hypertension	62.4	66.5	0.0001
Stroke/TIA	1.4	2.1	0.0104
Dementia	0.5	0.9	0.032
Obstructive airway disease	7.6	8.5	0.1171
Diabetes	23.7	28.6	<0.0001
Peripheral vascular disease	2.2	2.8	0.0786
Renal disease	2.7	3.9	0.0022
Cancer (nonmetastatic/ metastatic tumor)	1.4	1.8	0.1431
Atrial fibrillation	5.7	7.6	0.0005
Charlson comorbidity score			<0.0001
0	59.0	50.3	
1	12.4	13.9	
2	17.6	20.2	
3	7.2	9.1	
≥4	3.7	6.5	
Angiographic data			
Angiographic jeopardy score	3.9 ± 2.6	6.0 ± 2.8	<0.0001
Hospital duration			
Length of hospital stay, days	5 (4–7)	6 (4–8)	<0.0001

Values are %, mean ± SD, or median (interquartile range).

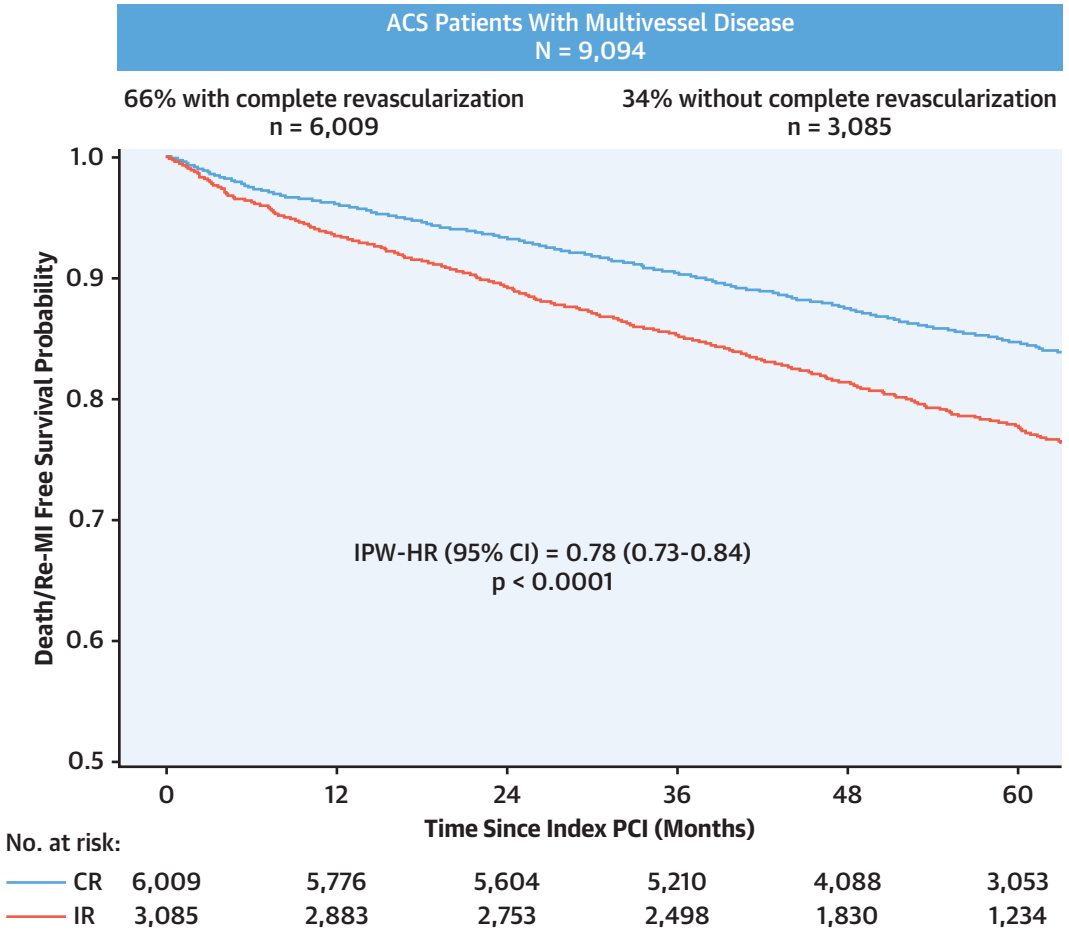
ACS = acute coronary syndrome; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; UA = unstable angina.

TABLE 2 Factors Associated With Complete Versus Incomplete Revascularization

	Odds Ratio (95% CI)	p Value
ACS type		0.0005
NSTEMI vs. UA	0.91 (0.78-1.06)	
STEMI vs. UA	0.78 (0.67-0.91)	
Age (per 10 yrs)	0.88 (0.84-0.92)	<0.0001
Sex (female)	1.12 (1.00-1.24)	0.044
Prior MI	0.61 (0.53-0.70)	<0.0001
Heart failure	0.68 (0.58-0.80)	<0.0001
Hypertension	0.91 (0.83-1.00)	0.056
Diabetes	0.82 (0.74-0.91)	0.0001

CI = confidence interval; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Kaplan-Meier Curves of the Primary Endpoint (All-Cause Death or Recurrent Myocardial Infarction) According to Treatment Strategy (Complete Revascularization Versus Incomplete Revascularization)**



Bainey, K.R. et al. J Am Coll Cardiol Intv. 2020;13(13):1557-67.

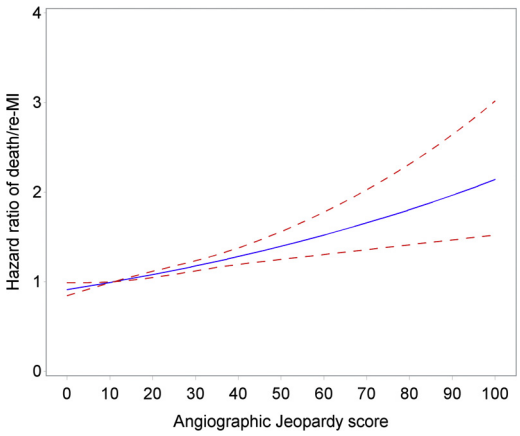
CI = confidence interval; CR = complete revascularization; IPW-HR = inverse probability-weighted hazard ratio; IR = incomplete revascularization; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Complete revascularization patients were younger and had lower rates of prior MI, heart failure, and CV risk factors such as hypertension and diabetes compared with incomplete revascularization patients. There were no differences in sex distribution. Patients with complete revascularization had lower baseline angiographic jeopardy scores and a shorter length of stay during the index ACS hospitalization.

FACTORS ASSOCIATED WITH COMPLETE REVASCULARIZATION IN ACS. As seen in Table 2, older age (adjusted odds ratio [aOR] per 10-year increment: 0.88; 95% CI 0.84 to 0.92; $p < 0.0001$), diabetes (aOR: 0.82; 95% CI: 0.74 to 0.91; $p < 0.0001$), prior MI (aOR: 0.61; 95% CI: 0.53 to 0.70; $p < 0.0001$), and heart failure (aOR: 0.68; 95% CI: 0.58 to 0.80; $p < 0.0001$) were significantly associated with a lower likelihood of complete revascularization; female sex (aOR: 1.12; 95% CI: 1.00 to 1.24; $p = 0.044$) was significantly associated with a higher likelihood of complete revascularization. Compared with patients with unstable angina, cardiac biomarker-positive patients with ACS were less likely to undergo complete revascularization (NSTEMI: aOR: 0.91 [95% CI: 0.78 to 1.06]; STEMI: aOR: 0.78 [95% CI: 0.67 to 0.91]; $p = 0.0005$).

MEDICATIONS WITHIN 6 MONTHS. The use of evidence-based secondary prevention therapies is

FIGURE 2 Association Between the Angiographic Jeopardy Score Following Percutaneous Coronary Intervention (Extent of Incomplete Revascularization) as a Continuous Variable and the Primary Outcome of All-Cause Death or Recurrent MI Expressed by the Hazard Ratio (95% Confidence Interval)



In the spline regression, a jeopardy score of 10% was taken as the reference point (hazard ratio: 1.0), and 4 knots were chosen at the 5th, 35th, 65th, and 95th percentiles of the distribution of the jeopardy score. **Blue line** denotes hazard ratio; **red dashed lines** denote 95% confidence interval. *Adjusted for age, sex, acute coronary syndrome type, and Charlson comorbidity score. MI = myocardial infarction.

shown in Supplemental Table S2. Both groups were well treated with optimal medical therapies for ACS. Overall, complete revascularization patients were just as likely to be treated with secondary prevention medications at 6 months as incomplete revascularization patients.

PRIMARY COMPOSITE ENDPOINT. The long-term primary composite of all-cause death or new MI was lower in complete revascularization patients compared with incomplete revascularization (**Central Illustration, Table 3**). The K-M estimate of the rate for primary composite event within 5 years was 15.4% in patients with complete revascularization compared with 22.2% in patients with incomplete revascularization, and the estimated risk reduction by complete revascularization relative to incomplete revascularization was an inverse probability-weighted HR (IPW-HR) of 0.78 (95% CI: 0.73 to 0.84; $p < 0.0001$).

SECONDARY COMPOSITE ENDPOINT. Complete revascularization patients also had a lower relative risk for the secondary composite of death, new MI, or repeat revascularization (K-M estimate of event rate within 5 years 23.3% vs. 37.5%; IPW-HR: 0.61; 95% CI: 0.58 to 0.65; $p < 0.0001$) (**Table 3**).

The components of the primary endpoint are shown in **Table 3**. Complete revascularization was associated with a reduction in all-cause death (K-M estimate within 5 years 9.2% vs. 14.8%; IPW-HR: 0.79; 95% CI: 0.73 to 0.86; $p = 0.0004$). In both groups, roughly one-half of deaths were CV. The 5-year CV death rate was reduced with complete revascularization (K-M estimate within 5 years 3.6% vs. 7.6%; IPW-HR: 0.64; 95% CI: 0.57 to 0.73; $p < 0.0001$). Complete revascularization patients had a lower risk for new MI (K-M estimate within 5 years 7.6% vs. 0.3%; IPW-HR: 0.76; 95% CI: 0.69 to 0.84; $p < 0.0001$). A significant reduction in risk for repeat revascularization alone was observed with complete revascularization (K-M estimate within 5 years 14.0% vs. 24.4%; IPW-HR: 0.53; 95% CI: 0.49 to 0.57; $p < 0.0001$).

CONTINUOUS RELATIONSHIP WITH ANGIOGRAPHIC JEOPARDY SCORE. When the extent of incomplete revascularization was examined as a continuous variable, there was a graded increase in the risk for all-cause death or new MI (primary composite outcome) within 5 years with increasing residual territory at risk, as measured by the post-PCI angiographic jeopardy score (**Figure 2**).

PRE-SPECIFIED SUBGROUPS. In our pre-specified subgroups (**Figure 3**), the primary composite HRs all favored complete revascularization. It is noteworthy that there were improved outcomes in men (p for interaction = 0.087) and those <75 years of age (p for interaction = 0.020). When stratified by coronary anatomy, complete revascularization was associated with a lower hazard of the primary composite regardless of anatomic subset (although higher event rates were noted with greater complexity of coronary disease). When examined by ACS presentation, complete revascularization was associated with a lower hazard of the primary composite irrespective of ACS type. Similarly, this was observed with or without diabetes. When stratified by renal disease status, complete revascularization was associated with a lower hazard of the primary composite without renal disease, but no statistical evidence for heterogeneity was noted (p for interaction = 0.48).

TIMING OF COMPLETE REVASCULARIZATION. To investigate the safety of outpatient staged complete revascularization, we evaluated whether the relative benefit of complete revascularization over incomplete revascularization in reducing all-cause death or new MI depends on the timing of complete revascularization. No difference in treatment effect was observed between the different staging groups: index complete revascularization (HR: 0.79; 95% CI: 0.72 to 0.87), in-hospital staged complete revascularization

TABLE 3 Clinical Outcomes Over Entire Follow-Up Period

	Event Rate Within 5 Years, % (95% CI)				
	Complete Revascularization	Incomplete Revascularization	Unadjusted HR (95% CI)	IPW-Adjusted HR (95% CI)	p Value
Primary composite outcome					
Death/new MI	15.4 (14.4–16.4)	22.2 (20.7–23.9)	0.66 (0.60–0.73)	0.78 (0.73–0.84)	<0.0001
Secondary composite outcome					
Death/new MI/ repeat revascularization	23.3 (22.2–24.4)	37.5 (35.7–39.3)	0.52 (0.52–0.60)	0.61 (0.58–0.65)	<0.0001
Other outcomes					
All-cause death	9.2 (8.4–10.0)	14.8 (13.5–16.2)	0.62 (0.55–0.70)	0.79 (0.73–0.86)	0.0004
New MI	7.6 (6.9–8.4)	10.3 (9.2–11.5)	0.70 (0.61–0.81)	0.76 (0.69–0.84)	<0.0001
Repeat revascularization	14.0 (13.1–14.9)	24.4 (22.8–26.0)	0.53 (0.48–0.59)	0.53 (0.49–0.57)	<0.0001
CV death/new MI	10.4 (9.6–11.3)	16.3 (14.9–17.7)	0.62 (0.55–0.69)	0.71 (0.65–0.77)	<0.0001
CV death	3.6 (3.2–4.2)	7.6 (6.7–8.8)	0.50 (0.42–0.59)	0.64 (0.57–0.73)	<0.0001

CV = cardiovascular; HR = hazard ratio; IPW = inverse probability-weighting; other abbreviations as in Figure 1.

(HR: 0.67; 95% CI: 0.47 to 0.95), and outpatient staged complete revascularization (HR: 0.38; 95% CI: 0.18 to 0.81) (p for interaction = 0.11).

DISCUSSION

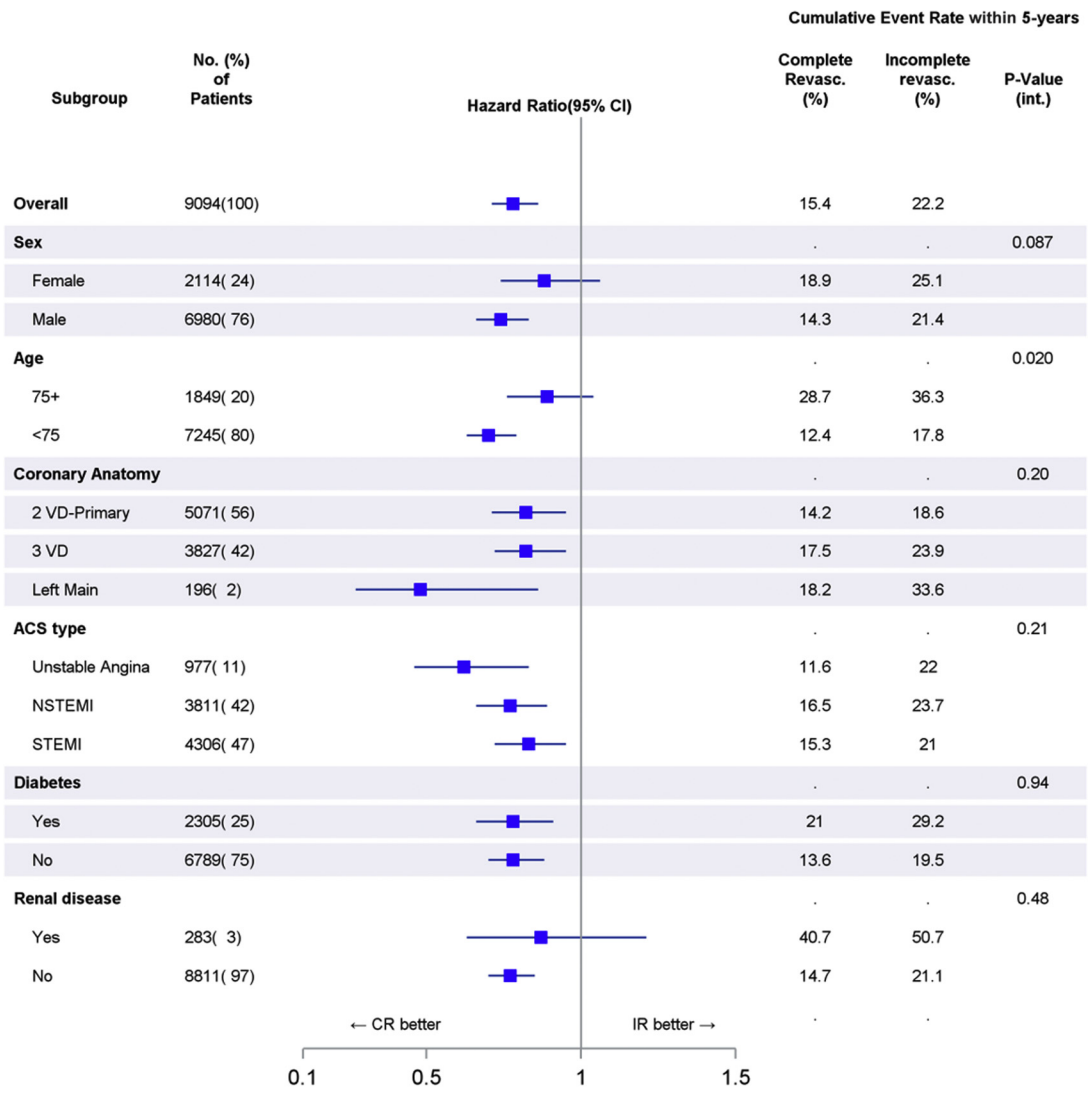
In this large prospective angiographic disease-based registry of patients with ACS with multivessel disease undergoing PCI, we found that complete revascularization occurs commonly and is associated with improved clinical outcomes. Achieving a residual angiographic jeopardy score of <10% (myocardium at risk) was associated with lower risk for all-cause death or new MI within 5 years. Furthermore, we have demonstrated a reduction in all-cause mortality (as well as CV death) with complete revascularization. On the contrary, an escalation of adverse events was observed with incomplete revascularization whereby the degree of jeopardized myocardium aligned proportionately with subsequent risk.

Following adjustment, complete revascularization was associated with a 22% reduction in the composite of death or recurrent MI long term. Moreover, similar reductions in death and MI alone were observed. As such, the benefits of complete revascularization are likely related to the treatment of nonculprit lesions as a preventive strategy to reduce long-term risk. As recently demonstrated in the optical coherence tomography substudy of the COMPLETE (Complete vs. Culprit-Only Revascularization to Treat Multi-Vessel Disease After Early PCI for STEMI) trial, roughly one-half of obstructive nonculprit lesions contain unstable plaque morphology and are prone to subsequent risk (16).

Unique to our study is the continuous relationship between post-PCI angiographic jeopardy score (residual myocardium at risk) and clinical outcome (all-cause mortality or new MI) within 5 years. This simple angiographic score has been shown as a validated prognostic myocardial metric and has performed with greater predictive value compared with the Jeopardy Score from Duke University and the Myocardial Jeopardy Index from BARI (13). With a myocardial jeopardy score of >10% (reference point 10%; HR: 1.00), we observed a near linear association with the risk for all-cause death or new MI long term.

Within our cohort, roughly one-third of patients with ACS did not undergo complete revascularization. Reported rates of incomplete revascularization in the New York Registry of more than 13,000 patients with multivessel disease undergoing PCI with bare-metal stents (1999 to 2000) was much higher (70.8%) (17). In SCAAR (Swedish Coronary Angiography and Angioplasty Registry), among 23,342 patients with multivessel disease undergoing PCI (2006 to 2010), the reported incomplete revascularization rate was 65.0% (8). However, more recently, data from the British Cardiac Intervention Society (2005 to 2015) revealed that roughly one-half of the cohort was incompletely revascularized (18). Although vessel complexity may contribute to incomplete revascularization (chronic total occlusions, angulated anatomy, calcified lesions, etc.), advanced tools and techniques in PCI now provide operators with the necessary skill set to perform complex PCI in a safe and efficient manner, allowing complete revascularization to be performed (19). It should be recognized almost two-thirds of our cohort underwent complete revascularization (higher than in other registries), recognizing the definition used for complete revascularization in our study and the

FIGURE 3 Pre-Specified Subgroup Analyses of the Primary Outcome



CI = confidence interval; Int. = interaction; IR = incomplete revascularization; LM = left main coronary artery; NSTEMI = non-ST-segment elevation myocardial infarction; VD = vessel disease; other abbreviations as in Figure 1.

exclusion of patients who underwent coronary artery bypass grafting (i.e., anatomy suited for PCI).

It is of interest to note the additional benefits of complete revascularization seen in men (p for interaction = 0.087) in our study, despite the higher likelihood that women will undergo complete revascularization. Lower mortality with complete revascularization in men has been observed in other clinical registries but primarily in STEMI (20,21). These sex-specific outcomes may be due to the characterization of coronary stenoses. Women tend to have fewer nonculprit lesions and may be less prone to plaque rupture (22). Moreover, women are less likely to have functionally significant lesions (despite angiographic appearance) on the basis of fractional flow reserve assessments (22). We also observed an association with improved outcomes in younger patients (<75 years of age) with complete revascularization (p for interaction = 0.020), which is likely reflective of unmeasured confounders (i.e., frailty) leading to incomplete revascularization.

In our angiographic analysis, benefits of complete revascularization were demonstrated regardless of anatomic disease burden. From a spectrum of 2-vessel disease to 3-vessel disease with left main coronary artery involvement, complete revascularization was associated with improved clinical outcomes within 5 years. However, the degree of anatomic disease burden itself did portend a worse prognosis, as higher events were noted with larger territories of myocardium at risk, consistent with prior studies (23,24). In a recent study of 41,639 New York Registry patients with multivessel disease, complexity of anatomic burden was associated with a higher risk for long-term mortality, particularly with incomplete revascularization (25).

Irrespective of ACS presentation type, complete revascularization was associated with improved clinical outcome within 5 years. In patients with NSTEACS with multivessel disease who undergo multivessel PCI, no randomized trials have been performed supporting complete revascularization. In a substudy of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, incomplete revascularization in patients with NSTEACS was associated with a higher rate of death, MI, or ischemia-driven unplanned revascularization, with a trend toward increased mortality (25). In a small retrospective study of 1,240 patients with NSTEACS, multivessel PCI compared with culprit-only intervention (with bare-metal stents) was associated with a reduction in death, recurrent MI, or revascularization at a median of 2.3-year follow-up (driven by a reduction in repeat revascularization) (25). Long-term survival (all-cause mortality) was recently demonstrated in a large cohort of patients with NSTEMI with multivessel disease from the British Cardiovascular Intervention Society PCI dataset with single-stage complete revascularization (18). In our study, complete revascularization in patients with NSTEACS was associated with a reduced risk for all-cause death or new MI long term compared with incomplete revascularization. These findings deserve confirmation in a large randomized study powered for hard clinical endpoints.

In patients with STEMI with multivessel disease, randomized studies have shown a reduction in clinical events with nonculprit PCI (either same sitting or staged). However, these benefits were driven largely by a reduction in repeat revascularization (26). Recently, the COMPLETE trial demonstrated a 26% reduction in CV death or new MI with staged nonculprit PCI compared with culprit-only intervention (5). Our results align with those of COMPLETE but address an entire spectrum of patients with ACS. Moreover, in the COMPLETE trial, it is interesting to note the consistent benefit of complete revascularization regardless of whether nonculprit PCI was performed during the index hospitalization (staged in hospital) (median 1 day) or several weeks after discharge (staged outpatient) (median 23 days), with no difference in event rates early after STEMI (27). As such, the risk of staged outpatient PCI in this context appears negligible. We also demonstrated no difference in treatment effect when considering the timing of PCI for complete revascularization. Analogous to coronary artery bypass surgery, the benefits of multivessel PCI appear to be accrued long term.

STUDY LIMITATIONS. Although our observational study was based on a robust, large, population-based cohort of patients with ACS with systematic angiographic data collection, we cannot exclude unmeasured variables as potential confounders in our analysis. As such, in is important to note that we report associations in outcomes (including all-cause mortality) that should be interpreted with caution. We did not exclude patients with chronic total occlusions or cardiogenic shock, which could limit the generalizability of our findings. Complex coronary anatomy precluding complete revascularization (i.e., diffuse severe disease or small vessel size not appropriate for PCI) could not be accurately assessed. Coronary stenoses were reported visually (i.e., without quantitative coronary angiography) by the interventional cardiologist following completion of the case, as is commonly done in clinical practice. We used an angiographic definition of complete revascularization that does not take into consideration functional findings based on ischemia or infarction. Finally, our analysis of patients with ACS was performed in a provincial, single-payer, government-funded health care system, and our results may not be generalizable to other health care systems internationally.

CONCLUSIONS

Results from this large angiographic disease-based registry of patients with ACS and multivessel disease undergoing PCI suggest that complete revascularization occurs commonly and is associated with improved clinical outcomes within 5 years, including a 21% reduction in all-cause mortality. Until further randomized data become available, our data support complete revascularization following ACS.

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PERSPECTIVES

WHAT IS KNOWN? In an observational angiographic disease-based registry of patients with ACS, complete revascularization with PCI compared with culprit-only intervention was associated with a reduction in the composite of all-cause mortality or new MI within 5 years.

WHAT IS NEW? Moreover, a 21% reduction in all-cause mortality was demonstrated.

WHAT IS NEXT? Future studies are required to understand the mechanism of benefit with complete revascularization following ACS, with a focus on imaging of nonculprit lesions to identify those with obstructive vulnerable plaques.

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KEY WORDS acute coronary syndromes, complete revascularization, multivessel disease, percutaneous coronary intervention

APPENDIX For a description of the APPROACH lesion score and supplemental tables, please see the online version of this paper.